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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/619,779

07/15/2003

Norihiro Kimoto

SHZ-015

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7590

02/24/2006

LAHIVE & COCKFIELD
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BOSTON, MA 02109

EXAMINER

PAK, YONG D

ART UNIT

PAPER NUMBER

1652

DATE MAILED: 02/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/619,779

Applicant(s)

KIMOTO ET AL.

Examiner

Yong D. Pak

Art Unit

1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 19 January 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-29 is/are pending in the application.
- 4a) Of the above claim(s) 6 and 8-29 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-5 and 7 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 15 July 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>1/16/04 7/15/03</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Claims 1-29 are pending. Claims 6 and 8-29 are withdrawn. Claims 1-5 and 7 are under consideration.

Election/Restrictions

Applicant's election without traverse of Group I (claims 1-5 and 7) in the reply filed on January 19, 2006 is acknowledged.

Claims 6 and 8-29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on January 19, 2006.

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d).

Information Disclosure Statement

The information disclosure statements (IDS) submitted on January 16, 2004 and July 15, 2003 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements are being considered by the examiner.

Claim Objections

Claim 7 is objected to because said claims depend from non-elected claim.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-5 and 7 are rejected under 35 U.S.C. 101 because the claimed invention is directed to a non-statutory subject matter.

Claims 1-5 and 7, as written, do not sufficiently distinguish over proteins as they exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products, such as being "isolated". In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. See *Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "isolated" as taught by the specification. See MPEP 2105.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 and claims 2-5 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

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Claim1 recite the phrases "reduces α -keto to produce (R)- α -hydroxy acid" and "reducing 2-chlorophenyl glyoxylic acid to produce (R)-2-chloromandelic acid". An enzyme doesn't "produce" a compound but converts a given compound into another compound. Examiner requests clarification of the above phrase and suggests deleting said the term "produce" in the above phrase.

Claim 1 and claims 2-5 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim1 recites the phrase "substantially fails to dehydrogenate". The metes and bounds of the phrase in the context of the above claim are not clear to the Examiner. It is not clear to the Examiner what is considered as "substantially failing" by the applicants. A perusal of the specification did not provide a clear definition for the above phrase. Without a clear definition, those skilled in the art would be unable to conclude if an enzyme "substantially fails" to dehydrogenate a compound without knowing the metes and bounds of the phrase.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 and 7 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

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reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-5 and 7 are drawn to a α -keto acid reductase having the properties and characteristics recited in the claims and "produced" by a microorganism *Leuconostoc mesenteroides subsp. dextranicum* (Examiner has interpreted the term "produced" broadly, to mean that the enzyme is produced as a constitutive protein as well as a recombinant protein with *L. mesenteroides* as a host cell). The claims encompass any or all recombinants, variants and mutants of any α -keto acid reductase from any source, any *Leuconostoc*. Therefore, the claims are drawn to a genus of polypeptides having any structure. The specification only teaches one species, the polypeptide of SEQ ID NO:2, isolated from *Leuconostoc mesenteroides subsp. dextranicum*, having α -keto acid reductase activity. This one species is not enough and does not constitute a representative number of species to describe the whole genus of any variants, recombinant and mutants of any α -keto acid reductase isolated from any source and "produced" in *Leuconostoc*, *Leuconostoc mesenteroides* or *Leuconostoc mesenteroides subsp. dextranicum* or any variants, recombinants and mutants of SEQ ID NO:2 and there is no evidence on the record of the relationship between the structure of a α -keto acid reductase of SEQ ID NO:2 and the structure of any recombinants, variants and mutants of any α -keto acid reductase or SEQ ID NO:2. Therefore, the specification fails to describe a representative species of the genus comprising any or all variants and mutants of SEQ ID NO:2 or any α -keto acid reductase isolated from any source,

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Leuconostoc, *Leuconostoc mesenteroides* or *Leuconostoc mesenteroides subsp. dextranicum*.

Claim 7 is also drawn to many functionally unrelated polypeptides encompassed within the scope of the claim, including partial sequences. The genus of these polypeptides comprise a large variable genus with the potentiality of encompassing many different polypeptides having different structure and activity or no activity. The specification only describes the polypeptide of SEQ ID NO:2, isolated from *Leuconostoc mesenteroides subsp. dextranicum*, having α -keto acid reductase activity. The specification fails to describe additional representative species of the polypeptides by any identifying characteristics or properties of the polypeptides, for which no predictability of function is apparent. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Given this lack of description of the representative species encompassed by the genus of the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the inventions of claims 1-5 and 7.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 1-5 and 7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the polypeptide of SEQ ID NO:2 having α -keto acid reductase activity and all the properties recited in the claims, does not reasonably provide enablement for any or all mutants and variants of any α -keto acid reductase isolated from any source and "produced" in *Leuconostoc*, *Leuconostoc mesenteroides* or *Leuconostoc mesenteroides subsp. dextranicum* and having all the properties recited in the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1-5 and 7 are drawn to a α -keto acid reductase "produced" by *Leuconostoc*, *Leuconostoc mesenteroides* or *Leuconostoc mesenteroides subsp. dextranicum* and having the properties and characteristics recited in claims 1-2. Therefore, the claims are drawn to polypeptides having any structure. Therefore, the breadth of these claims is much larger than the scope enabled by the specification.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of α -keto acid reductase including variants and mutants and any or all variants and mutants of SEQ ID NO:2, broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the polypeptide of SEQ ID NO:2, isolated from *Leuconostoc mesenteroides subsp. dextranicum*, having α -keto acid reductase activity. It would require undue experimentation of the skilled artisan to make and use the claimed variants and mutants of SEQ ID NO:2 or α -keto acid reductase from other sources. The specification is limited to teaching the use of a α -keto acid reductase of SEQ ID NO:2 but provides no guidance with regard to the making of variants and mutants or with regard to other uses. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure, the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by this claim.

While enzyme isolation techniques, recombinant and mutagenesis techniques are known, and it is routine in the art to screen for multiple substitutions or multiple modifications as encompassed by the instant claims, the specific amino acid positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass any or all recombinants, variants and mutants of any α -keto acid reductase from any source, any *Leuconostoc*, *Leuconostoc mesenteroides* or *Leuconostoc mesenteroides subsp. dextranicum* and any or all recombinants of SEQ ID NO:2 having any activity or no activity, because the specification does not establish: (A) regions of the protein structure which may be modified without affecting α -keto acid reductase activity; (B) the general tolerance of α -keto acid reductase to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Claim 7 also broadly encompass variants, mutants and recombinants having α -keto acid reductase activity, but polypeptides having any function or having no function.

Therefore, the breadth of these claims is much larger than the scope enabled by the specification.

The function of a polypeptide cannot be predicted from its structure and the specification does not teach how to use polypeptides having any function or having no activity. The quantity of experimentation in this area is extremely large since there is significant variability in the activity of the polynucleotides in the claims. It would require significant study to identify the actual function of the encoded polypeptides and identifying a use for the encoded polypeptide would be an inventive, unpredictable and difficult undertaking. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

The art is extremely unpredictable with regard to protein function in the absence of realizable information regarding its activity. Even very similar proteins may have every different functions. In the current case, where no specific information is known regarding the function, it is entirely unpredictable what function and activity will be found for the protein. The prior art does not resolve this ambiguity, since no prior art activity is identified for the encoded polypeptides.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any or all recombinants, variants and mutants of any α -keto acid reductase from any source. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19

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24 (CCPA 1970)). Without sufficient guidance, determination of mutants, variants and recombinants of SEQ ID NO:2 or any α -keto acid reductase from any source having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –
(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5 and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Morris et al.

Claims 1-5 and 7 are drawn to a α -keto acid reductase isolated from *Leuconostoc mesenteroides* subspecies *dextranicum* and having the properties and characteristics recited in claims 1-2.

Leuchtenberger et al. (US Patent No. 4,609,623 – form PTO-892) discloses an enzyme isolated from *Leuconostoc dextranicum*, wherein the enzyme reduces α -keto acids to (R)- α -hydroxyl acid using reduced NAD⁺ (Column 1, lines 56 through Column 2, line 68). *Leuconostoc dextranicum* is a synonym for *Leuconostoc mesenteroides* subsp. *dextranicum* (See Taxonomy browser (*Leuconostoc mesenteroides* subsp. *dextranicum*) – form PTO-892). The enzyme of Leuchtenberger et al inherently

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possesses the same material structure and functional characteristics of the enzyme of claims 1-2 since both enzymes are isolated from *Leuconostoc mesenteroides* subsp. *dextranicum* and have α -keto acid reductase activity. Since the Office does not have facilities for examining and comparing applicant's enzyme with the enzyme of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the enzyme of the prior art does not possess the same material structure and functional characteristics of the claimed enzyme). Therefore, the reference of Leuchtenberger et al. anticipates claims 1-5 and 7.

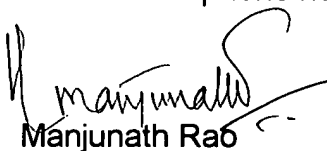
None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935. The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned are 571-273-8300 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Yong D. Pak
Patent Examiner 1652


Manjunath Rao
Primary Patent Examiner 1652